



## Ketamine

Approximately one-third of individuals with major depressive disorder (MDD) do not respond to available antidepressant medications and are considered to have treatment-resistant depression (TRD). Current therapies mainly target monoaminergic systems and have a delayed onset of effect.

Several studies have shown rapid antidepressant efficacy with IV ketamine. Proposed mechanisms of ketamine's antidepressant action include *N*-methyl-*D*-aspartate receptor (NMDAR) modulation, GABAergic interneuron disinhibition, direct effects of its hydroxyl-norketamine (HNK) metabolites, and numerous downstream actions. These proposed mechanisms of action may complement each other to improve symptoms of depression by increasing activity at excitatory synapses in affective-regulating brain circuits.

Currently, the Food and Drug Administration (FDA) has only approved ketamine hydrochloride injection (Ketalar) for the induction and maintenance of general anesthesia. Because of increased interest in the off-label use of ketamine infusions for the treatment of mood disorders, the American Psychiatric Association (APA) Council of Research Task Force on Novel Biomarkers and Treatments recently published a consensus statement, the intent of which is to provide guidance on issues and considerations associated with this relatively new therapy. The consensus statement is not meant to serve as an absolute standard or guideline because the APA does not believe that there is enough high-quality evidence to support such a policy. **The following is a summary of the issues discussed in the consensus statement and its supplement.**

### *Patient selection*

There are no formal indications for the use of ketamine in the treatment of psychiatric disorders but the strongest data are in its use in patients with MDD without psychotic features. Most of these studies only measure antidepressant efficacy during the first week following a single infusion of ketamine but some investigations assess the efficacy of repeated dosing over longer time periods. The consensus statement recommends that the following measures be taken.

- 1 A comprehensive diagnostic assessment should be completed to establish current diagnosis and evaluate history of substance use and psychotic disorders.
- 2 Assessment of baseline symptom severity should be completed to allow later assessments of clinical change with treatment<sup>a</sup>
- 3 A thorough history of antidepressant treatment should be collected and documented to confirm previous adequate trials of antidepressant treatments

- 4 A thorough review of systems should be performed to evaluate potential risk factors associated with ketamine treatment<sup>b</sup>
- 5 Decisions on the specific physical examination and laboratory screening assessments should be made according to established guidelines and advisories issued by the American College of Cardiology Foundation/American Heart Association and the American Society of Anesthesiologists and should be based on a patient's individual clinical characteristics<sup>c</sup>
- 6 A careful review of past medical and psychiatric records and/or corroboration of the past history by family members are strongly encouraged; all current medications and allergies should be reviewed, including histories of opiate and benzodiazepine use; the use of a baseline urine toxicology screen is strongly encouraged to ensure the accuracy of the reported substance use and medication record
- 7 An informed consent process, including discussion of the risks associated with the treatment,<sup>d</sup> the limits of the available information pertaining to the potential benefits of the treatment, the fact that this is an off-label use of ketamine, and a discussion of alternative treatment options should be completed; this discussion should be complemented with written materials, and the patient should provide written informed consent before initiating treatment.

<sup>a</sup> Self-report versions of the Inventory of Depressive Symptomatology and Quick Inventory of Depressive Symptomatology (<http://counsellingresource.com/quizzes/depression-testing/qids-depression/>) are examples of scales that are available at no cost to clinicians and researchers.

<sup>b</sup> This review should also include questions pertaining to functional exercise capacity, which has been demonstrated to provide a good screening tool for patients that are at increased risk for adverse events associated with anesthesia exposure and surgical procedures.

<sup>c</sup> American College of Cardiology Foundation and the American Heart Association guidelines for perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery and practice advisory from the American Society of Anesthesiologists.

<sup>d</sup> The Ketalar package insert provides essential information related to risk of ketamine administration.

### *Clinician experience and training*

Currently, there are no pre-defined training requirements that clinicians must meet before administering sub-anesthetic doses of ketamine.

When used to treat depression, intravenous (IV) ketamine is usually dosed 0.5 mg/kg and given over 40 minutes, resulting in peak plasma concentrations between 70 to 200 ng/ml. These plasma concentrations are not high enough to produce general anesthesia, which requires peak plasma concentrations between 2000-3000 ng/ml and are lower than those associated with waking up from ketamine anesthesia (500-1000 ng/ml).

When administered to patients with depression who are in other ways generally healthy, a 40-minute infusion of IV ketamine 0.5 mg/kg does not appear to significantly affect respiratory status. However, the therapy could impact blood pressure and heart rate. Wan and colleagues (2015) studied 84 otherwise healthy patients with depression who received a total of 205 infusions of ketamine hydrochloride 0.5 mg/kg per 40 minutes IV. No significant changes in oxygen saturation were observed but transient mean (SD) peak increases in systolic (19.6 [12.8] mm Hg) and diastolic (13.4 [9.8] mm Hg) were reported during the infusions. Approximately 30% of patients experienced blood pressures  $\geq$  180/100 mm Hg or pulses  $\geq$  110 beats per minute. **Because of these potential cardiovascular complications, the APA consensus statement recommends that clinicians who provide 40-minute IV infusions of ketamine hydrochloride 0.5 mg/kg be licensed to administer a Drug Enforcement Administration (DEA) Schedule III medication and possess Advanced Cardiac Life Support certification.**

During ketamine treatment, some patients experience prominent transient dissociative or psychotomimetic effects. Clinicians must be proficient in the behavioral management of patients with marked mental status changes and the treatment of emergency behavioral situations. Before discharge, an on-site clinician needs to evaluate the patient for psychiatric risks, including suicidal ideation. Treating clinicians also need to ensure that swift psychiatric follow-up is available after discharge should the need arise.

Clinicians also need to acquire experience with the method of ketamine administration. Local community standards of practice and/or clinical practice committees should determine the substance of this experience. One resource for the development of these standards is the American Society of Anesthesiologists' *Statement on Granting Privileges for Administration of Moderate Sedation to Practitioners Who Are Not Anesthesia Professionals*.

### *Treatment Setting*

**There is little evidence to support the use of any specific monitoring methods for mitigating the risks associated with sub-anesthetic doses of ketamine. Treatment facilities should be prepared to monitor basic cardiovascular (electrocardiogram, blood pressure) and respiratory (oxygen saturation or end-tidal CO<sub>2</sub>) status. They should also be able to administer oxygen to patients with reduced respiratory function and restrain patients whose behavior endangers themselves or others. Treatment facilities need a plan for how to manage sustained alterations in cardiovascular function, such as the provision of advanced cardiac life support or transfer to an inpatient setting that deals with acute cardiovascular events. When pretreatment evaluation identifies higher risk patients, these should undergo treatment at a facility appropriately equipped and staffed to manage any cardiovascular or respiratory events that may occur.**

## *Medication Delivery*

### Dose

Most clinical trials and case reports have used the 0.5 mg/kg per 40 minutes IV dose of ketamine hydrochloride. Although other doses and infusion rates have been studied, the authors of the Consensus Statement do not believe that there is sufficient information to “allow any meaningful analysis of any specific dose or route of treatment compared with the standard dose of 0.5 mg/kg per 40 minutes IV.” However, they state that “the use of alternative doses and routes of administration could be appropriate for individual patients under specific conditions”.

One such circumstance is patients whose BMI is 30 or greater. In the Wan study (which utilized the 0.5 mg/kg per 40 minutes IV regimen), greater hemodynamic changes were seen in patients whose BMI was 30 or higher. Calculating a patient’s ideal body weight (IBW) and basing the ketamine dose on that IBW may be safer in this patient population but this has not been well studied.

### Delivery Procedure

The Consensus authors strongly recommend the development of site-specific standard operating procedures (SOP). The SOP **before the infusion** should include

- (1) Confirmation of pre-procedural evaluation and informed consent
- (2) Assessment of baseline vital signs, including blood pressure, heart rate, and oxygen saturation or end-tidal CO<sub>2</sub>
- (3) Criteria for acceptable baseline vital signs before initiation of medication delivery
  - a. If SBP  $\geq$ 150 mmHg or DBP  $\geq$ 95 mmHg at baseline, treatment of hypertension should be considered
  - b. If HR < 60 bpm or > 100 bpm, relative risks of treatment should be considered
  - c. Baseline SpO<sub>2</sub> should be > 94
- (4) Incorporation of a “time-out” procedure in which the name of the patient and correct dosing parameters are confirmed

SOPs must also describe how patients’ physiological and mental status will be monitored **during the infusion**. This includes

- (1) Assessment of respiratory status (ie, oxygen saturation or end tidal CO<sub>2</sub>)
- (2) Assessment of cardiovascular function (blood pressure and heart rate, reported on a regular basis)
  - a. Goal SBP < 180 mmHg, DBP < 110 mmHg at all times during the infusion
  - b. Age adjusted maximum heart rates
    - i. 20 yo < 140 bpm, 30 yo < 133, 40 yo < 126, 50 yo < 119, 60 yo < 112
- (3) Assessment of level of consciousness
  - Modified Observer’s Assessment of Alertness/Sedation Scale

- (4) Delineation of criteria for stopping the infusion and a plan for handling cardiovascular or behavioral events during treatment
  - a. Pallor, cyanosis, or any symptoms suggesting poor perfusion
  - b. Shortness of breath, wheezing
  - c. Chest, jaw or arm pain
  - d. Patient's desire to stop

**After the infusion**, clinicians must ensure that patients' physiological and mental status has returned to baseline. Outpatients treated with ketamine will need a responsible adult to drive them home. Follow-up procedures should be reviewed with an emphasis on how a patient will quickly contact an appropriately trained clinician should the need arise.

### *Follow-up and Assessments*

#### Efficacy Measures of Short-term Repeated Administration

Most of the ketamine literature is comprised of studies that last less than one month.

In a two week, randomized, placebo-controlled trial conducted in 68 patients with treatment-resistant major depressive disorder, Singh and colleagues evaluated the efficacy of twice versus thrice weekly ketamine administration (0.5 mg/kg per 40 minutes IV). There was little difference in efficacy between the two treatment regimens. After two weeks of twice-weekly treatment, 69% of individuals responded (versus 15% of placebo patients) and 37.5% of patients remitted (versus 7.7% of placebo patients). After two weeks of thrice-weekly treatment, 53.8% of patients responded (versus 6% of placebo patients) and 23.1% of patients remitted (versus 0% of placebo patients).

Some patients entered an open-label phase that lasted an additional two weeks. These individuals continued their original ketamine schedule (either twice or thrice weekly). The average reduction in MADRS score was 27 points for the 13 individuals who received four weeks of ketamine twice- weekly versus 23 points for the 13 patients who received four weeks of ketamine thrice-weekly. **The results of this trial suggest that twice-weekly administration is as efficacious as thrice-weekly for a period of up to four weeks.**

There are a few reports of patients not responding until the fourth ketamine infusion but the question of when to declare a patient "ketamine resistant" remains unanswered. Cusin and colleagues studied the efficacy of increased doses in patients who had failed to respond to standard IV ketamine dosing (0.5 mg/kg per 40 minutes). See below.

#### Efficacy of Longer-term Repeated Administration

A significant downside to the use of ketamine to treat mood disorders is the lack of data on its long-term effectiveness and safety. This must be discussed with patients during the preprocedural informed consent process. Some clinics are providing a two or three-week course of ketamine given two or three times per week, followed by a taper period and/or additional treatments based on observed duration of response. However, other than a few case series, there are no published data that support sustained efficacy with ongoing treatment. Because of

the potential risks associated with long-term exposure to ketamine, clinicians must consider the relative benefit of each ketamine infusion.

### *Safety Measures and Continuation of Treatment*

Chronic high-frequency ketamine use has been associated with cognitive impairment but **studies that have examined the cognitive effects of sub-anesthetic doses of ketamine have not demonstrated adverse cognitive effects.** Individuals receiving ongoing ketamine for the treatment of mood disorders should undergo periodic cognitive testing; however, there is no agreed upon type or frequency of evaluation. **Cystitis** has also been reported with chronic high-frequency ketamine use. Clinicians should ask individuals receiving ongoing ketamine infusions about urinary symptoms and pelvic pain.

The development of **ketamine use disorder** in patients receiving ongoing treatment is a serious concern and clinicians should use the fewest number of treatments necessary to bring about the desired response. If abuse is suspected, providers should test patients' urine and ask if the individual has sought additional treatments at other facilities.

**By the second month of treatment, if once weekly dosing does not produce the desired clinical response, the consensus authors recommend stopping ketamine.**

The studies described below evaluate **maintenance therapy with iv ketamine.**

### ***Wilkinson et al., 2018***

Wilkinson and colleagues report on the outcomes of 54 patients with severe and treatment-resistant mood disorders who received multiple ketamine infusions at the ECT suite of the Yale Psychiatric Hospital. From October 2014 to February 2017, clinicians at this facility provided off-label ketamine on a case-by-case basis to individuals who did not qualify for research protocols. The main reasons for their failure to qualify were as follows: disallowed comorbid conditions (general medical and/or psychiatric), evidence of ultra-refractoriness (failing numerous previous treatment trials or ECT), current hospitalization, inability to delay treatment long enough to complete required study procedures (medication washout, observation periods), presence of significant suicidal ideation or behavior, age outside of protocol limits.

Ketamine 0.5 mg/kg was mixed in 500 ml of 0.9% normal saline and infused over 40 minutes. Ideal body weight was used for patients whose BMI  $\geq 30$  kg/m<sup>2</sup>. Patients remained on their psychotropic medications but took them after ketamine on the days of treatment; clinicians tried to avoid benzodiazepines in the 8-1 hour period before the infusion. Both inpatients and outpatients were treated. Outpatients were not allowed to drive on the day of treatment and had to meet the following criteria: (1) return to predose hemodynamic parameters, (2) Clinician-Administered Dissociative State Scale (CADSS) score of 0 (or  $\leq$  pretreatment score), (3) at least 30 minutes of observation after the end of the infusion. For patients whose response was not sustained, the clinicians attempted to develop an individualized, symptom-triggered tapering regimen, the

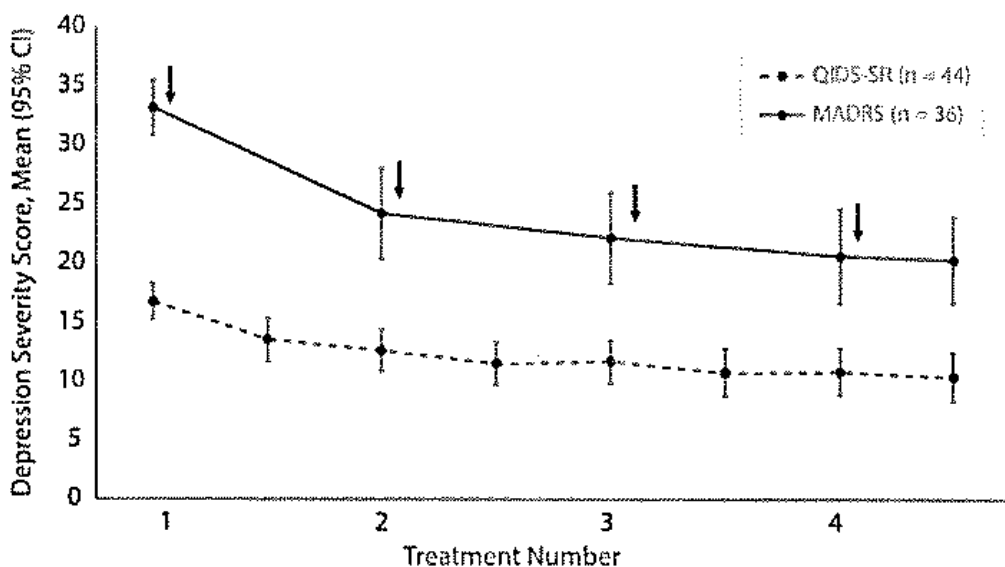
goal of which was to maintain response while giving ketamine every three or four weeks. The CogState battery ([www.cogstate.com](http://www.cogstate.com)) was performed at baseline and every 6-12 treatments.

During the 29 month study period, 54 patients (16-87 yo, mean age = 46.7) were treated with at least one ketamine infusion and a total of 518 infusions were given. Approximately 80% of the patients had major depressive disorder and the average baseline QIDS-SR score was 19.8 (6.0). Half had been treated with ECT and 65% had a history of hospitalization for suicidal ideation or attempt.

#### Acute Phase

Forty-four (44) of the 54 total patients suffered from a primary mood disorder and completed an acute treatment period, which consisted of four infusions over two weeks. Response was defined as 50% or greater improvement in QIDS-SR and remission was defined as QIDS-SR score  $\leq 5$ . After the first infusion, 31.8% ( $n = 14$ ) of patients responded and 11.4% ( $n = 5$ ) remitted. By the fourth infusion, 45.5% ( $n = 20$ ) responded and 27.3% ( $n = 12$ ) remitted. **The majority of the improvement occurred between the first and second infusions.** Five patients dropped out of the acute phase—four because of lack of efficacy and one because of inability to tolerate the infusions.

Figure 1. Depression Severity Over Time in a 4-Infusion Ketamine Protocol<sup>a</sup>



<sup>a</sup>Last observation carried forward was used for missing data. A mixed-effects, general linear model showed a main effect of time using the QIDS-SR (main effect of time:  $t = -7.72$ ,  $P < .001$ ) as well as the MADRS ( $t = -8.48$ ,  $P < .001$ ). Treatments were given twice weekly. Time points between treatments were 2–4 days; the QIDS-SR was administered 24 hours following each treatment. Arrows indicate ketamine infusions.

Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, QIDS-SR = Quick Inventory of Depressive Symptomatology-Self Report.

With regard to dissociative effects in the acute phase, the mean (SD) CADSS score was 6.79 (8.51) at 40 minutes and nearly zero at 70-80 minutes (mean [SD] score = 0.12 [0.32]). Following the second, third, and fourth infusion, mean (SD) CADSS scores at 40 minutes were 5.86 (6.25), 4.52 (5.03) and 4.53 (7.16), respectively. At 70-80 minutes, mean CADSS scores were 0.07 (0.26), 0.04 (0.19), and 0.00 (0.00), respectively.

#### *Continuation/maintenance phase*

Fourteen (14) patients received continuation/maintenance ketamine treatment that lasted at least 14 weeks (range 14-126 weeks). Overall, 351 treatments were administered. The average number of treatments per patient was 25.1 (10.5) and the mean length of course of treatment was 75.7 (39.2) weeks. **Not including the acute phase of four treatments given twice per week, the mean (SD) time between treatments was 22.3 days (22.7).** One (1) patient experienced tachyphylaxis, remitting after the acute phase but relapsing when the infusions were tapered to every two weeks. No clinical improvement was seen even after twice weekly therapy was restarted. Two (2) patients relapsed and required hospitalization after attempting suicide. After ketamine twice weekly was restarted, both recovered response status. Seven (7) patients relapsed (depression score < 25% improvement from baseline) but were able to recover response status. One (1) patient moved to another state for six months but responded partially after a second acute series of ketamine treatment. Three (3) individuals did not relapse during longer-term follow-up. **Qualitatively, 7 of these 14 patients said that ketamine's antidepressant effect started to fade approximately 3 weeks after an infusion.**

The CogState battery was performed at baseline and every 6-12 treatments thereafter. There was no correlation between number of infusions and change in cognition. Neither cystitis nor increased psychosis were observed. Other than one of the 14 patients who was dismissed from the program because of cannabis abuse, there was no indication of increased drug-seeking behavior.

**Archer and colleagues (2018)** performed a retrospective case series of patients with TRD who received acute and maintenance IV ketamine infusions at a hospital in Canada. The investigators defined TRD as a depressive disorder diagnosis (unipolar or bipolar), failure of at least five antidepressants, refractory to psychotherapy, and refractory to or unable to undergo ECT. Exclusion criteria included psychosis, primary personality disorder, substance use disorder, or uncontrolled medical condition. Ketamine was given at a dose of 0.5 mg/kg, infused for 40 minutes. The institution's ketamine protocol required the following baseline labs: CBC, creatinine, electrolytes, TSH, liver enzymes, 12-lead electrocardiogram.

During the one-year review period (January 1, 2016-December 31, 2016), 30 patients underwent an acute course of IV ketamine. The acute phase consisted of twice weekly infusions for either six or eight treatments. Based on response in the acute phase, the treating psychiatrist decided which patients would benefit from maintenance therapy; **the treating psychiatrist determined the frequency and number of treatments during the maintenance phase on a case by case**

**basis.** Most patients continued their existing medication regimens during both phases of the study. Patients completed the Beck Depression Inventory II (BDI-II) before each infusion. No specific BDI-II cutoffs were used in determining eligibility for maintenance therapy—rating scale scores were just one part of the overall evaluation of response.

Of the 30 patients who received acute treatment, 11 (10 females) entered the maintenance phase. The patients ranged in age from 31 to 69 years, eight had unipolar depression (three had bipolar depression), and all had received at least one course of ECT. The total number of treatments ranged from 10 to 51; total length of treatment ranged from 6 to 49 weeks.

All patients who entered the maintenance phase experienced a decrease in BDI-II scores during the acute phase. In all patients, the median maintenance and final BDI-II score were lower than the baseline BDI-II score. **However, only 4 of the 11 patients demonstrated median maintenance and final BDI-II scores  $\leq$  the post-acute BDI-II score.** At the end of the one-year period, only 4 of the 11 patients were continuing maintenance ketamine infusions.

Nursing staff used a tracking sheet to monitor vital signs and side effects. All patients experienced transient side effects during the infusions. These included heart rate and blood pressure elevations, feeling faint, drowsiness, blurred vision, headache, dry mouth, restlessness, feelings of dissociation, changes in perception of stimuli, difficulty concentrating. One patient discontinued maintenance treatment because of dissociative symptoms and irritability which subsided a couple of days after the infusions. There were no reported lab abnormalities or cognitive or urinary side effects.

The authors concluded that maintenance ketamine treatments may be appropriate for a select subset of patients.

The studies summarized below evaluate the effects of **iv ketamine's effects in patients with suicidal ideation** and **escalating iv ketamine doses**.

### ***Wilkinson et al., 2017***

Wilkinson and colleagues examined the effects of a single dose of intravenous ketamine on suicidal ideation (si) in patients with major depression, PTSD, and bipolar disorder. Researchers extracted individual patient data from studies published between January 1, 2000 and November 15, 2016; included studies were required to have used either saline or midazolam as a control. Inclusion criteria included active or passive suicidal ideation, which was defined as a score  $\geq 2$  on MADRS item 10 ("weary of life/fleeting suicidal ideation") or a score  $\geq 1$  on the HAM-D suicidal ideation item ("feels life is not worth living"). For self-report scales, si was defined as a score of  $\geq 1$  on QIDS-SR item 12 ("I feel that life is empty or wonder if it's worth living") or a score  $\geq 1$  on the Beck Depression Inventory (BDI) item 9 ("I have thoughts of killing myself, but I would not carry them out").

Ten trials were included in the meta-analysis. One hundred sixty-seven patients (167) from these trials met the criteria for baseline si. Average baseline rating scale scores were as follows: MADRS score = 33.4, HAM-D = 20.5, QIDS-SR =

17.7, BDI = 29.2. About 48% of patients were receiving psychotropic medications. The primary outcome measures were the suicide items from the above listed rating scales, obtained for up to one week after ketamine administration.

**In depressed patients with si, iv ketamine reduced si within one day and the effect lasted up to a week.** Compared with control treatments, ketamine had significant benefits on the individual suicide items of the MADRS, HAM-D, and the QIDS-SR but not the BDI. Ketamine's effects on si were partially independent of its effect on mood.

### ***Cusin et al., 2017***

In an open-label study, Cusin and colleagues attempted to assess (1) the clinical antidepressant safety and efficacy of two-step repeated intravenous dose ketamine augmentation in outpatients with TRD and (2) the duration of ketamine's antidepressant efficacy as augmentation to ongoing antidepressants for three months after the final infusion.

Patients were required to stay on their current antidepressant medication regimen for 4 weeks prior to the start of the study and the duration of the trial period. Inclusion criteria were (1) age 18-65 years; (2) primary diagnosis of MDD; (3) HAM-D<sub>28</sub> score  $\geq 20$  at screening; (4) history of three or more failed antidepressant treatment trials of adequate dose/duration during the current episode (including current regimen); (5) SI for more than 3 months, as measured by the Columbia-Suicide Severity Rating Scale (C-SSRS), without the requirement for immediate hospitalization; (6) score on HAM-D<sub>28</sub> suicide item  $\geq 2$  (current SI, thoughts of own death). Exclusion criteria were (1) pregnancy; (2) unstable medical illness; (3) bipolar disorder; (4) past multiple adverse drug reactions; (5) psychotic illness; (6) substance use disorder within 1 year; (7) positive urine toxicology; (8) past history of ketamine abuse and (9) SI requiring immediate hospitalization or immediate risk.

Study participants received the infusions at Massachusetts General Hospital's Clinical Research Center (CRC) where an anesthesiologist and a psychiatrist were present during all infusions. Side effects and vital signs were monitored 30 minutes prior to the infusion, every 5 minutes during the infusion, and for 2 hours afterwards by the nursing staff. Before being discharged home under the care of a responsible adult, patients were taken from the CRC to the outpatient psychiatry clinic for further evaluation by a psychiatrist or psychologist. For three weeks, patients received twice weekly infusions for a total of six treatments. The initial dose was 0.5 mg/kg administered over 45 minutes. **After Infusion 3, if a participant's HAM-D<sub>28</sub> score did not improve by at least 30%, the dose was increased to 0.75 mg/kg for Infusions 4, 5, and 6.**

Fourteen individuals (14) met inclusion criteria and 12 completed all six infusions. The mean baseline HAM-D<sub>28</sub> score was  $28.6 \pm 4.8$ . Participants were taking an average of  $1.9 \pm 1.0$  antidepressants,  $1.9 \pm 1.7$  other psychotropic medications (mood stabilizers, atypical antipsychotics, benzodiazepines) and, in the current

episode, had failed  $8.3 \pm 5.7$  previous antidepressant trials. Six of the 14 (42.9%) had failed an adequate course of ECT either in the current episode or lifetime.

After the completion of three ketamine infusions, 7.1% (1/14) of patients responded. Of patients who completed all six infusions, 5/12 (41.7%) met criteria for response and 2/12 (16.7%) met criteria for remission. **The authors concluded that there was more pronounced improvement during the higher dose phase.** See Figure 1.

During the three-month follow-up, patients were seen every two weeks. **One of the five responders maintained response for six weeks after the final infusion but the other four responders relapsed within two weeks.**

No serious adverse events were reported and both doses were well tolerated. The most common side effects were mild in nature and included the following: visual and auditory disturbances (buzzing sounds), dissociative symptoms, drowsiness, sedation, headache, and nausea. Most of these resolved within one to two hours after the end of the infusion. All patients experienced at least a 10 mmHg elevation in systolic blood pressure during the infusion but there were no significant changes in pulse or oxygen saturations.

### ***Ionescu et al., 2018***

In a double-blind, randomized, placebo-controlled study, Ionescu and colleagues studied medicated outpatients with severe MDD with chronic SI. Twenty-six (26) outpatients were randomized to six ketamine infusions (0.5 mg/kg over 45 minutes) or saline placebo over three weeks. Researchers assessed depression and SI at baseline, 240 minutes' post-infusion, and during a three-month follow-up phase.

During the three-week infusion phase, there were no differences in depression severity or SI between ketamine and placebo. At the end of the three weeks, two ketamine patients and one placebo patient met remission criteria. At three-month follow-up, two patients in each group met remission criteria. The authors concluded that outpatients with severe TRD and chronic SI may require more than 0.5 mg/kg of intravenous ketamine.

Given that intravenous ketamine administration may not be feasible in outpatient settings, researchers have begun exploring the **intranasal route**.

### ***Lapidus et al., 2014***

In a randomized, double-blind, cross-over, proof of concept trial, Lapidus et al. studied intranasal ketamine in adults (age 21-65) with depression. Participants had to have failed at least one prior antidepressant (AD) trial in the current episode and were allowed to continue stable doses of psychotropics (including AD) throughout the study. Inclusion criteria included a diagnosis of Major Depressive Disorder (MDD), chronic or recurrent, without psychotic features and a baseline score  $\geq 30$  on the Inventory of Depressive Symptomatology-Clinician Rated (IDS-C). Exclusion criteria included the following: unstable medical/neurological condition, axis I

disorder other than MDD, high risk of suicide, substance abuse/dependence in past 6 months, psychotic disorder, bipolar disorder, developmental disorder, lifetime abuse/dependence on ketamine/phencyclidine.

The study consisted of two seven-day treatment periods; treatment periods were at least seven days apart. To progress from the first to the second treatment period, participants had to have an IDS-C score  $\geq 24$ . **An anesthesiologist in a clinical research unit provided the 20 minute administration of either 50 mg of racemic ketamine hydrochloride or placebo (0.9% saline solution).** Study drug or placebo was provided in identical syringes, containing clear solutions of either 100 mg/ml ketamine in 0.9% saline or saline alone. An LMA MADgic mucosal atomization device (LMA North America, Inc., San Diego, CA) was used to provide 5 intranasal applications of solution (volume 100  $\mu$ l), separated by five minutes. Each of five ketamine applications provided 10 mg of study drug.

Vital signs (heart rate, blood pressure, respiration, and pulse oximetry) were continuously monitored for at least four hours in the research unit following treatment. In the original protocol, participants remained in the research unit overnight but after safety was shown, the protocol was changed to allow for discharge four hours after treatment with outpatient follow-up.

**The primary outcome was change in the Montgomery-Asberg Depression Rating Scale (MADRS) at 24 hours following intervention.** In each treatment period, assessments occurred at +40 min, +120 min, +240 min, +24 h, + 48 h, +72 h, and +7 days following treatment administration. Secondary outcomes included change in the Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR) and Hamilton Anxiety Rating Scale (HAM-A) and the proportion of participants meeting response ( $\geq 50\%$  decrease in MADRS from baseline) or remission (MADRS  $\leq 9$ ) criteria.

Safety and tolerability were evaluated using the following instruments: Brief Psychiatric Rating Scale-Positive sub-scale (BPRS+), Clinician-Administered Dissociative States Scale (CADSS), mood item of the Young Mania Rating Scale (YMRS), Systematic Assessment for Treatment Emergent Effects (SAFTEE). Clinically significant changes were defined as systolic or diastolic blood pressure  $> 180/100$  mmHg or heart rate  $> 110$  beats/minute. Management of adverse effects was provided per protocol or as believed necessary by the treating anesthesiologist.

Twenty individuals qualified for the study and were randomized to one of two treatment orders: ketamine-placebo or placebo-ketamine. Two participants withdrew consent and did not participate in both treatment periods. Thus, 18 patients completed both treatment periods and were included in the modified intent to treat (mITT) sample.

Table One summarizes demographic and clinical characteristics of the study participants.

Characteristic	Value
Participants treated, n (%)	20 (100)
Gender (M/F)	10/10
Age at enrollment (yrs)	<b>48.0 <math>\pm</math> 12.8</b>

Characteristic	Value
Race (%)	
<i>Caucasian</i>	<b>18/20 (90)</b>
<i>Asian</i>	1/20 (5)
<i>Black</i>	0/20 (0)
<i>Other</i>	1/20 (5)
Hispanic (%)	3/20 (15)
Married (%)	6/20 (30)
Employed (%)	10/20 (50)
Age of Onset	21.4 ±12.0
Illness Duration in Years	<b>27.4 ± 13.7</b>
Length of Current Episode in Years	<b>15.2 ±17.4</b>
Failed Antidepressant Medications	4.1 ± 3.9
History of ECT (%)	4/20 (20)
History of Psychotherapy (%)	17/19 (89)
History of Suicide Attempts (%)	2/20 (10)
Past Substance Use Disorder (%)	3/20 (15)
Current Anxiety Disorder (%)	4/20 (20)
Melancholic (%)	9/20 (45)
Atypical (%)	2/20 (10)
Baseline IDS-C (Screen)	<b>42.7 ± 8.5</b>

### Results

Compared to placebo, ketamine administration was associated with significant improvement of depressive symptoms at the 24 hour post-intervention time point. The estimated mean difference in MADRS score was  $7.6 \pm 3.7$  (95% CI: 3.9-11.3). Response was defined as a 50% drop in MADRS score. **Twenty-four hours after ketamine administration, 8/18 (44%) of participants responded; 24 hours after placebo administration, 1/18 (6%) responded. Improvement in depressive symptoms was not sustained and there was no significant difference at 72 hours or seven days.** With regard to secondary outcomes, ketamine administration was associated with significant improvement on the QIDS-SR and HAM-A at the 24-hour time point. Mean difference in QIDS-SR was  $3.0 \pm 2.4$  (95% CI: 1.1-4.9). Mean difference in HAM-A was  $4.5 \pm 3.2$  (95% CI: 1.4-7.6).

Intranasal ketamine was associated with small increases on measures of psychosis (BPRS+) and dissociation (CADSS). No relationship was found between antidepressant response and ketamine associated changes in dissociative or psychotomimetic symptoms. Four participants experienced treatment-emergent increases in systolic blood-pressure > 130 mm Hg following ketamine compared to three following placebo. No patients had a diastolic blood pressure > 100 mm Hg. All hemodynamic changes resolved four hours post infusion and there was no association between antidepressant response and hemodynamic changes. The most common adverse events related to ketamine administration were feeling

strange/unreal, poor memory, weakness/fatigue. **There were no serious adverse events and most resolved within four hours.**

### ***Daly et al., 2018***

Daly and colleagues conducted a phase 2, double-blind, doubly randomized, delayed-start, placebo-controlled study of intranasal esketamine adjunctive to oral antidepressant therapy—the first clinical study to date of intranasal esketamine for TRD. Esketamine, the *S*-enantiomer of ketamine, has a higher affinity for the NMDA receptor than the *R*-enantiomer and rapid antidepressant efficacy has been shown with its intravenous administration.

Participants were medically stable adults (20-64 years) with a diagnosis of MDD (DSM-IV-TR). All had TRD, defined as inadequate response to 2 or more antidepressants (with at least 1 inadequate response in the current episode). Inclusion criteria included a score of  $\geq 34$  on the 30-item, clinician-rated Inventory of Depressive Symptomatology, which corresponds to moderate to severe depression. Exclusion criteria included the following: recent or current suicidal ideation with intent to act, suicidal behavior, or homicidal ideation or intent, diagnosis of bipolar or related disorders, intellectual disability, psychotic disorder, MDD with psychosis, PTSD, OCD, substance/alcohol use disorders in the past year, recent use of cannabis.

Study participants continued on established oral antidepressant therapy. A disposable nasal spray device contained 200  $\mu\text{L}$  of solution (ie, 2 sprays). Each device provided either esketamine hydrochloride, 16.14 (14 mg of esketamine base) per 100  $\mu\text{L}$  spray or placebo. On each dosing day during phase 2, participants self-administered 1 spray of study drug into each nostril at 3 points, each separated by 5 minutes. During phase 3, participants self-administered 1 spray of esketamine into each nostril at 1, 2, or 3 points (28, 56, or 84 mg), each separated by 5 minutes.

The study was conducted in multiple outpatient referral centers and included **four phases**:

- (1) screening (n=126)
- (2) double-blind treatment (days 1-15), **made up of two 1-week periods**
- (3) optional open-label treatment (days 15-74)
- (4) post-treatment follow-up (8 weeks).

See Figure 1. At the beginning of double-blind treatment, 67 patients were randomized (3:1:1:1) to intranasal placebo or esketamine 28, 56, or 84 mg, twice weekly (days 1 and 4). Thirty-eight of these 67 patients were women, mean [SD] age = 44.7 [10.0] years.

At the end of period 1, 28 of 33 placebo patients (85%) continued to have moderate to severe symptoms (QIDS-SR<sub>16</sub> total score  $\geq 11$ ). These 28 patients were re-randomized (1:1:1:1) to intranasal esketamine 28 mg, 56 mg, or 84 mg or

placebo twice weekly (days 8 and 11). Placebo patients who had mild or no symptoms at the end of period 1 continued placebo (n=4).

Regardless of response in the double-blind phase (phase 2), all study participants had the option of entering the open-label phase (phase 3), the purpose of which was to evaluate the efficacy of less-frequent intranasal esketamine dosing. Sixty of 67 patients (90%) completed periods 1 and 2 and 57 patients entered the open-label phase (phase 3). Esketamine 56 mg was administered on day 15 and investigators adjusted subsequent doses (range, 28-84 mg) based on their clinical judgment. **Administration was twice weekly for the first 2 weeks, weekly for the next 3 weeks, then every 2 weeks thereafter.**

**The primary efficacy end point was change from baseline (pre-dose, day 1 in each period) to end point (day 8 in each period) in MADRS total score.**

The MADRS was performed on days 1 (predose and 2 hours postdose), 2, 8 (predose), 9 and 15.

Before ketamine administration and at 40 minutes and two hours post-dose, researchers assessed the following safety measures: vital signs, the Clinician Administered Dissociative States Scale (CADSS), 4 item positive symptom subscale from the Brief Psychiatric Rating Scale (BPRS).

### *Results*

In all 3 esketamine groups, change (least squares mean [SE] difference vs placebo) in MADRS total score (both periods combined) was superior to placebo (esketaamine 28 mg: -4.2 [2.09],  $p = 0.02$ ; 56 mg: -6.3 [2.07],  $p = 0.001$ ; 84 mg: -9.0 [2.13],  $p < 0.001$ ). In the open label phase, improvement was sustained (-7.2 [1.84]) even though intranasal ketamine was dosed less frequently. **At the end of the open-label phase (74 days), approximately 65% of remaining patients were classified as responders (decrease in MADRS total score  $\geq 50\%$ ) and 32.4% met remission criteria (MADRS total score  $\leq 10$ ).** See Figures 2 and 3. During the double-blind phase, three individuals who received nasal esketamine left the study because of adverse events (versus none receiving placebo). These events included syncope, headache and dissociative syndrome. During the open-label phase, one individual left the study because of an adverse event (ectopic pregnancy).

### ***Canuso et al., 2018***

In a double-blind, randomized, multicenter, proof-of-concept study, Canuso and colleagues evaluated the efficacy of standard-of-care (SOC) treatment plus intranasal esketamine or placebo in patients with MDD at imminent suicide risk.

Sixty-eight (68) individuals were randomly assigned to receive esketamine 84 mg or placebo twice weekly (in addition to standard care) for four weeks. Participants were individuals aged 19-64 years who had presented to an emergency department or inpatient psychiatric unit. Inclusion criteria included: diagnosis of MDD without psychotic features according to DSM-IV-TR criteria and confirmed by the Mini International Neuropsychiatric Interview (MINI); affirmative response to MINI question B5 ("Think about suicide [killing yourself]?") in the present and B9

("Intend to act on thoughts of killing yourself?") in the past 24 hours; score  $\geq 22$  on the MADRS on day 1 before dosing; voluntary agreement to SOC treatment, including hospitalization (5 days after randomization unless treating physician determined that longer/shorter period was warranted) and initiation or optimization of one or more non-investigational antidepressants. Exclusion criteria included a current diagnosis of bipolar disorder, moderate to severe substance use disorder, intellectual disability, antisocial personality disorder, borderline personality disorder, current/past diagnosis of a psychotic disorder.

The study consisted of four weeks of db treatment (days 1 to 25) followed by eight weeks of posttreatment follow-up (days 26 to 81). During the four week db phase, participants were randomized to receive either twice-weekly intranasal esketamine 84 mg or matching placebo in addition to SOC. Randomization was stratified by study center and type of SOC antidepressant (monotherapy or AD plus augmentation therapy). Under the supervision of a health care provider, participants self-administered the study drug via a nasal spray device. Each device held 200 uL of solution (i.e., two sprays, each 100 uL spray delivering 14 mg of esketamine or placebo). Three nasal sprays were required to deliver 84 mg of esketamine; a bittering agent was added to the placebo to help mask treatment assignment. **The primary efficacy endpoint was change in MADRS score from baseline to four hours after initial dose. Clinicians' global judgment of suicide risk was also assessed using the Suicide Ideation and Behavior Assessment Tool.** After hospital discharge, outpatient appointments occurred twice weekly through day 25 of db treatment. During posttreatment follow-up (days 26 to 81), study participants only received SOC antidepressant treatment. Appointments were weekly through day 52 and biweekly through day 81.

Most randomized participants (49/68) completed the db treatment phase and entered post-treatment follow-up, which 44 individuals completed. Baseline MADRS score was 38.5 (6.17) and 38.8 (7.02) in the esketamine and placebo groups, respectively. At 4 and 24 hours, a significantly greater improvement in MADRS score was observed in the esketamine group compared to the placebo group (least-square mean difference = - 5.3, SE = 2.10, effect size = 0.61; least-square mean difference = -7.2, SE = 2.85, effect size = 0.65). At day 25, the difference in improvement between the two groups was not significant (least-square mean difference = - 4.5, SE = 3.14, effect size = 0.35. See Figure 2.

Patients who received esketamine experienced significantly greater improvement on the MADRS suicidal thoughts item score at 4 hours (effect size = 0.67) but not at 24 hours (effect size = 0.35) or at day 25 (effect size = 0.29). See Figure 3.

A clinician global judgment of suicide risk score of 0-1 was thought to indicate a resolution of suicide risk. In a post-hoc analysis, a greater number of participants in the esketamine group (compared to the placebo group) achieved resolution of suicide risk at 4 hours (21.2% vs 9.7%) and 24 hours (40.0% vs 6.5%) after the first dose. See Figure 4.

Nasal esketamine was generally well tolerated. The most common adverse events in patients who received esketamine were nausea, dizziness, dissociation, unpleasant taste, and headache. Five patients in the esketamine group dropped

out of the db phase because of adverse events. These were agitation, aggression, unpleasant taste, and ventricular extrasystoles in one participant each and dizziness/dyspnea/nausea in one participant. Transient elevations in blood pressure were observed the esketamine group across all dosing days (maximum mean increase from predose measurement: systolic, 16.7 mmHg (SD= 10.46), compared with 8.7 mm Hg (SD = 7.48) for the placebo; diastolic, 11.9 mm Hg (SD = 8.88) compared with 7.6 mm Hg (SD = 9.35) for the placebo group. Blood pressure elevations peaked at 40 minutes after dosing and returned to pretreatment levels within 2 hours after dosing. Dissociative symptoms (CADSS) peaked at 40 minutes after dosing, resolved by 2 hours, and lessened with repeated dosing.

## **Conclusions and Recommendations**

Ketamine provides rapid relief for many patients with TRD and when given under appropriate supervision, both the intravenous and intranasal routes of administration seem generally well tolerated. For patients who do respond well to standard antidepressants, ketamine could provide fast relief while the medication is reaching its full effect. Significant downsides to ketamine's use include its abuse potential and lack of information about long-term efficacy and optimal dosing strategies. More studies are clearly needed and Johnson & Johnson is currently seeking FDA approval for the use of intranasal esketamine in patients with major depression who are treatment resistant and/or acutely suicidal. If ketamine is used in HHSC state operated facilities, I would suggest adherence to the recommendations of the 2017 APA Consensus Statement.

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